DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, Maryland 20857

OCT 28 1999

Richard A. Shupack, Esq.
U.S. Regulatory Affairs
Elan Pharmaceuticals
800 Gateway Blvd.
South San Francisco, CA 94080

Re: Docket No. 98P-1191/CP1 and PSA1

Dear Mr. Shupack:

This letter responds to your citizen petition and petition for stay of action dated December 15, 1998, and supplemented January 15, 1999. Your petitions pertain to the requirements for generic drugs referencing Naprelan (naproxen sodium) controlled release tablets. You request that FDA require that abbreviated new drug applications (ANDAs) referencing Naprelan include (1) additional pharmacokinetic data to demonstrate equivalent early onset of analgesic effect, and (2) additional evidence of equivalence (not merely pharmacokinetic data) with respect to the absence of potential excessive gastrointestinal (GI) toxicity (specifically, results of comparative scintigraphy or endoscopy studies) or other evidence that adequately addresses the GI toxicity issue. In your petition for stay of action, you request that FDA stay the decision on whether to approve any ANDA that references Naprelan until either the Agency acts on the citizen petition or an ANDA meets the standards requested in the citizen petition. For the reasons discussed below, your citizen petition is denied.

I. Background

Naprelan is a controlled release dosage form of naproxen sodium, a nonsteroidal anti-inflammatory drug (NSAID). The controlled release tablet dosage form is patented and uses the proprietary IPDAS (Intestinal Protective Drug Absorption System) technology. Naprelan combines a mixture of naproxen sodium available as 30 percent immediate release and 70 percent coated with a polymer designed to release slowly over time. Naprelan is usually administered as two 375-mg tablets (750 mg) once daily, or two 500-mg tablets (1000 mg) once daily. A new drug application (NDA 20-353) for Naprelan was approved in 1996. Naprelan is approved for use in the treatment of acute gout, ankylosing spondylitis, tendinitis, bursitis, osteoarthritis, rheumatoid arthritis, relief of mild to moderate pain, and primary dysmenorrhea.

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II. ANDA applicants do not need to submit additional pharmacokinetic data to demonstrate equivalent early onset of analgesic effect

You state that Naprelan's "unique" release profile using the proprietary IPDAS microparticles combined with immediately available naproxen ensures the early onset of analgesia,[1] thereby supporting the indications for the relief of mild to moderate pain and in the treatment of primary dysmenorrhea (Petition at 5). You state that because Naprelan's labeling includes indications requiring early onset of analgesia, the labeling of a proposed ANDA must also include those indications (Petition at 6). You also claim that bioequivalence studies in the ANDA must demonstrate that the proposed drug provides the same early onset of analgesia as Naprelan (Petition at 6).

The Federal Food, Drug, and Cosmetic Act (the Act) requires that an ANDA contain information to show that the generic product is bioequivalent to the reference listed drug and that the labeling proposed for the generic drug is the same as the labeling approved for the listed drug (section 505(j)(2)(A) of the Act). An ANDA for an extended release product that has an extended release product as its reference listed drug should demonstrate that the proposed generic product is both pharmaceutically equivalent and bioequivalent to the listed drug. See FDA's guidance, *Oral Extended (Controlled) Release Dosage Forms In Vivo Bioequivalence and In Vitro Dissolution Testing.*

There is no question that rate of pain relief is highly correlated to the rate of absorption of a drug product. Your contention here, however, is that the uniqueness of the technology used in the dosage form necessitates a level of comparison not used for other combined immediate release and controlled release products. There is nothing unique about the fundamental principle of this technology, i.e., coating one portion of the total amount of drug with an insoluble/semisoluble/or pH dependent polymer or coating. A number of such controlled release mechanisms exist and have been approved by the Agency. Although the specific polymer used may be unique, the principle is well established.

You claim that a bioequivalence study to support an ANDA for controlled release naproxen cannot demonstrate equivalence to Naprelan in early onset of analgesia unless it includes measurements of naproxen bioavailability at 15 minutes, and that the single-dose fasting study specified in the guidance for immediate release (IR) naproxen would not provide sufficient information (Petition at 6). That study calls for naproxen levels to be measured in blood samples taken at 30, 60, and 90 minutes in the first part of the sequence. You also claim there is no basis to assume that equivalence of naproxen blood levels at 30 minutes produces an analgesic response within 30 minutes as demonstrated by the study in the Naprelan NDA (Petition at 6).

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[1] In the NDA for Naprelan, Elan submitted a clinical study demonstrating relief of acute postoperative pain supporting the addition of this indication to the approved labeling.

Normally, the time of onset of analgesia is roughly correlated to the peak drug concentration in the blood (C_{max}) and the time to peak drug concentration in the blood (T_{max}). In the case of Naprelan, as a function of the controlled release dosage form design, T_{max} does not occur until almost 3.5 hours after dosing and well after an analgesic response has been achieved. This designed performance of the overall dosage form calls into question the ability of C_{max} or T_{max} to be a discriminating test of bioequivalence with respect to acute analgesic performance. In theory, some other measure could be used to ensure analgesic equivalence or similarity between the upstroke in plasma levels from time zero to peak (e.g., point-to-point analysis, a partial area-under-the-curve (AUC) comparison). Current FDA policy is to compare the total AUC of the plasma level time curves. Equivalent naproxen blood levels of generic products and Naprelan at 30 minutes would be expected to produce an equivalent analgesic response in the same time. Bioequivalence studies for generic versions of this drug product would be expected to meet the appropriate confidence intervals for AUC and C_{max}.

It should be noted that in 9 of 10 pharmacokinetic studies in the NDA for Naprelan, the initial plasma level sampling schedule was predose, and 0, 0.5, 1, 2, . . . hours post dosing. If the initial rate of drug absorption was critical to the product, this should have been demonstrated in the NDA. Although it is useful to measure more plasma levels during the early part of the plasma level time curve, the fact that the NDA sponsor did not measure plasma levels at 15 minutes in the vast majority of its pharmacokinetic studies, including those conducted in support of changes in the Naprelan formulation is a strong indication that such data are not needed in an ANDA.

As stated previously, ANDA applicants referring to Naprelan as the reference listed drug must provide evidence demonstrating that their extended release naproxen product is bioequivalent to Naprelan. More specific sampling schedules than those provided in the Naprelan NDA pharmacokinetic studies are not necessary to meet the bioequivalence requirements of 21 CFR 320.21.

III. Additional evidence of equivalence with respect to the absence of potential excessive GI toxicity is not required

GI toxicity is a recognized safety issue with the use of NSAIDs. The following is included in the approved labeling for Naprelan under the heading "Special Studies":

> In a double-blind randomized, parallel group study, 19 subjects received either two Naprelan 500 mg tablets (1000 mg) once daily or naproxen 500 mg tablets (1000 mg) twice daily for 7 days. Mucosal biopsy scores and endoscope scores were lower in the subjects who received Naprelan. In another double-blind, randomized, crossover study, 23 subjects received two Naprelan 500 mg tablets (1000 mg) once daily, naproxen 500 mg tablets (1000 mg) twice daily and aspirin 650 mg four times daily (2600 mg) for 7 days each. There were significantly fewer duodenal erosions seen with Naprelan than with either naproxen or aspirin.

> There were significantly fewer gastric erosions with both Naprelan and naproxen than with aspirin. The clinical significance of these findings is unknown.

As you note, endoscopic studies by themselves do not prove either that naproxen's GI toxicity is the result of topical exposure to the drug as opposed to a systemic effect of the drug, or that endoscopic scores necessarily correlate with clinical toxic effects. However, you claim the analysis of clinical toxicity in naproxen studies submitted in the Naprelan NDA and celecoxib studies included in the recently approved Celebrex labeling support the clinical significance of endoscopic studies[2] and their role in the safety assessment of any NSAID product (Petition Supplement at 6).

You state that the reduced GI toxicity of Naprelan is a direct result of the proprietary IPDAS vehicle system, which disperses naproxen throughout the GI system (Petition at 3). You also state that the endoscopy studies of Naprelan do not demonstrate that the release profile produced by the proprietary IPDAS tablet is safer than a specific, different release profile. You also claim that the endoscopy studies demonstrate a probable correlation between the release profile of naproxen dosage forms and the degree of naproxen related GI toxicity (Petition at 11).

We do not agree that the endoscopy studies demonstrate a correlation between the release profile of naproxen and the degree of naproxen related GI toxicity. Without an IV administration study to compare the results of the bioavailability/absorption patterns and measurements of systemic toxicity, the true relationship between naproxen dosage forms and endoscopic results cannot be determined. At present, these additional endoscopy studies are not needed to evaluate bioequivalence.

You also state that, at a minimum, ANDAs should contain a scintigraphy study (radiochemical quantitation) that can assess the site integrity of the dosage unit within the GI tract and confirm critical parameters such as disintegration time and food impact as included in the current Naprelan labeling (Petition at 16). As stated above, the principle behind the proprietary IPDAS system is not unique. Many other similar controlled release schemes exist and have been approved by the Agency. Moreover, the gamma scintigraphy study results included in the Naprelan NDA that you claim demonstrate that Naprelan disperses naproxen throughout the GI system were not considered validated data during the review of the original NDA, and we do not consider them validated now. The gamma scintigraphy study was in fact added as a secondary objective to a food-fasting trial. It was included in the final label for informational purposes, not to set a new review standard. Requiring ANDA applicants to perform such a study is not scientifically or legally justified. The Agency has approved other ANDAs for controlled and sustained release products (e.g., verapamil, metronidazole, nifedipine) and for products that

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[2] The Celebrex labeling also includes the following disclaimer: "The correlation between findings of endoscopic studies, and the relative incidence of clinically serious upper GI events that may be observed with different products, has not been fully established."

exhibit GI toxicity (e.g., sulindac, metronidazole, diclofenac) without requiring additional evidence of safety beyond that required of the innovator product and without compromising public health.

You contend that there is a reasonable basis to conclude that the composition of differently formulated once-a-day naproxen dosage units raises serious questions of safety regarding the relationship between naproxen, the mechanism by which once-a-day naproxen release is achieved, and GI toxicity of a potentially serious nature (Petition at 18).

The mechanism of action by which NSAIDs cause GI toxicity is far from clear. Parenteral NSAIDs that have been approved since the 1980s in the United States and abroad are associated with GI adverse effects similar to those seen with orally administered products. Therefore, it cannot be determined that the release profile of a once-daily naproxen tablet affects GI toxicity as measured by endoscopic scores and that the differences in endoscopic scores are caused by the different release profiles of different naproxen dosage forms as claimed. Naprelan is not labeled as more efficacious or safer from the GI perspective than any other naproxen dosage form. Approved ANDAs referencing Naprelan will have the same labeling as Naprelan.

IV. Conclusion

For the reasons described above, FDA denies your requests that FDA require that ANDAs referencing Naprelan include additional pharmacokinetic data to demonstrate equivalent early onset of analgesic effect, and that FDA require in such ANDAs additional evidence of equivalence (not merely pharmacokinetic data) with respect to the absence of potential excessive GI toxicity (specifically results of comparative scintigraphy or endoscopy studies) or other evidence that adequately addresses the GI toxicity issue. No ANDA referencing Naprelan has been approved as of the date of this response, so your petition for stay of action has been effectively granted.

Sincerely,

/s/

Dennis E. Baker
Associate Commissioner
for Regulatory Affairs